

FILE 'HOME' ENTERED AT 08:03:00 ON 15 APR 2010

=> index bioscience

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS

| SINCE FILE | TOTAL   |
|------------|---------|
| ENTRY      | SESSION |
| 0.22       | 0.22    |

FULL ESTIMATED COST

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 08:03:18 ON 15 APR 2010

63 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view search error messages that display as 0\* with SET DETAIL OFF.

=> s retin? (s) (pml/rar or pml-rar)

- 12\* FILE ADISCTI
- 2\* FILE ADISINSIGHT
- 1\* FILE ADISNEWS
- 7\* FILE AGRICOLA
- 1\* FILE ANABSTR
- 0\* FILE ANTE
- 0\* FILE AQUALINE
- 0\* FILE AQUASCI
- 32\* FILE BIOENG
- 233\* FILE BIOSIS
- 7\* FILE BIOTECHABS
- 7\* FILE BIOTECHDS
- 289\* FILE BIOTECHNO
- 6\* FILE CABA
- 430\* FILE CAPLUS
- 0\* FILE CEABA-VTB
- 0\* FILE CIN
- 8\* FILE CONFSCI
- 0\* FILE CROPB
- 0\* FILE CROPU
- 0\* FILE DDFB

<-----User Break----->

=> s retin? (s) (pml/rar or pml-rar#)

- 14\* FILE ADISCTI
- 2\* FILE ADISINSIGHT
- 2\* FILE ADISNEWS
- 7\* FILE AGRICOLA
- 1\* FILE ANABSTR
- 0\* FILE ANTE
- 0\* FILE AQUALINE
- 0\* FILE AQUASCI
- 47\* FILE BIOENG
- 280\* FILE BIOSIS
- 12\* FILE BIOTECHABS
- 12\* FILE BIOTECHDS
- 327\* FILE BIOTECHNO
- 6\* FILE CABA
- 473\* FILE CAPLUS
- 0\* FILE CEABA-VTB
- 0\* FILE CIN
- 8\* FILE CONFSCI

```

0* FILE CROPB
0* FILE CROPU
0* FILE DDFB
60* FILE DDFU
53* FILE DGENE
17* FILE DISSABS
0* FILE DRUGB
0* FILE DRUGMONOG2
90* FILE DRUGU
5* FILE EMBAL
305* FILE EMBASE
397* FILE ESBIODBASE
0* FILE FOMAD
0* FILE FROSTI
0* FILE FSTA
3* FILE GENBANK
34 FILES SEARCHED...
0* FILE HEALSAFE
10* FILE IFIPAT
0* FILE IMSDRUGNEWS
4* FILE IMSPRODUCT
1* FILE IMSRESEARCH
0* FILE KOSMET
204* FILE LIFESCI
162* FILE MEDLINE
1* FILE NTIS
0* FILE OCEAN
284* FILE PASCAL
0* FILE PCTGEN
13* FILE PROMT
0* FILE PROUSDDR
0* FILE PS
0* FILE RDISCLOSURE
276* FILE SCISEARCH
0* FILE SYNTHLINE
241* FILE TOXCENTER
0* FILE USGENE
194* FILE USPATFULL
0* FILE USPATOLD
36* FILE USPAT2
0* FILE VETB
0* FILE VETU
0* FILE WATER
6* FILE WPIDS
0* FILE WPIFV
62 FILES SEARCHED...
6* FILE WPINDEX

```

35 FILES HAVE ONE OR MORE ANSWERS, 63 FILES SEARCHED IN STNINDEX

L1 QUE RETIN? (S) (PML/RAR OR PML-RAR#)

=> s L1 (s) degrad?

```

0* FILE ADISCTI
1* FILE ADISINSIGHT
0* FILE ADISNEWS
2* FILE AGRICOLA
0* FILE ANABSTR
0* FILE ANTE
0* FILE AQUALINE

```

```

0* FILE AQUASCI
7* FILE BIOENG
18* FILE BIOSIS
1* FILE BIOTECHABS
1* FILE BIOTECHDS
30* FILE BIOTECHNO
1* FILE CABA
31* FILE CAPLUS
0* FILE CEABA-VTB
0* FILE CIN
1* FILE CONFSCI
0* FILE CROPB
0* FILE CROPU
0* FILE DDFB
8* FILE DDFU
0* FILE DGENE
23 FILES SEARCHED...
0* FILE DISSABS
0* FILE DRUGB
0* FILE DRUGMONOG2
15* FILE DRUGU
0* FILE EMBAL
30* FILE EMBASE
58* FILE ESBIODBASE
0* FILE FOMAD
0* FILE FROSTI
0* FILE FSTA
0* FILE GENBANK
0* FILE HEALSAFE
0* FILE IFIPAT
0* FILE IMSDRUGNEWS
0* FILE IMSPRODUCT
0* FILE IMSRESEARCH
0* FILE KOSMET
22* FILE LIFESCI
10* FILE MEDLINE
0* FILE NTIS
0* FILE OCEAN
37* FILE PASCAL
0* FILE PCTGEN
2* FILE PROMT
0* FILE PROUSDDR
0* FILE PS
0* FILE RDISCLOSURE
27* FILE SCISEARCH
0* FILE SYNTHLINE
12* FILE TOXCENTER
0* FILE USGENE
44* FILE USPATFULL
0* FILE USPATOLD
9* FILE USPAT2
0* FILE VETB
0* FILE VETU
0* FILE WATER
1* FILE WPIDS
0* FILE WPIFV
1* FILE WPINDEX

```

24 FILES HAVE ONE OR MORE ANSWERS, 63 FILES SEARCHED IN STNINDEX

L2 QUE L1 (S) DEGRAD?

=> s L3 (s) (apl or (acute (2a) promylelocytic))

L3 NOT FOUND

The L-number entered could not be found. To see the definition of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s L2 (s) (apl or (acute (2a) promylelocytic))

- 0\* FILE ADISCTI
- 1\* FILE ADISINSIGHT
- 0\* FILE ADISNEWS
- 2\* FILE AGRICOLA
- 0\* FILE ANABSTR
- 0\* FILE ANTE
- 0\* FILE AQUALINE
- 0\* FILE AQUASCI
- 6\* FILE BIOENG
- 6\* FILE BIOSIS
- 0\* FILE BIOTECHABS
- 0\* FILE BIOTECHDS
- 26\* FILE BIOTECHNO
- 1\* FILE CABA
- 9\* FILE CAPLUS
- 0\* FILE CEABA-VTB
- 0\* FILE CIN
- 0\* FILE CONFSCI
- 0\* FILE CROPB
- 0\* FILE CROPU
- 0\* FILE DDFB
- 4\* FILE DDFU
- 0\* FILE DGENE

23 FILES SEARCHED...

- 0\* FILE DISSABS
- 0\* FILE DRUGB
- 0\* FILE DRUGMONOG2
- 8\* FILE DRUGU
- 0\* FILE EMBAL
- 10\* FILE EMBASE
- 44\* FILE ESBIODBASE
- 0\* FILE FOMAD
- 0\* FILE FROSTI
- 0\* FILE FSTA
- 0\* FILE GENBANK
- 0\* FILE HEALSAFE
- 0\* FILE IFIPAT
- 0\* FILE IMSDRUGNEWS
- 0\* FILE IMSPRODUCT
- 0\* FILE IMSRESEARCH
- 0\* FILE KOSMET
- 18\* FILE LIFESCI
- 4\* FILE MEDLINE
- 0\* FILE NTIS
- 0\* FILE OCEAN
- 25\* FILE PASCAL
- 0\* FILE PCTGEN
- 1\* FILE PROMT
- 0\* FILE PROUSDDR
- 0\* FILE PS
- 0\* FILE RDISCLOSURE
- 8\* FILE SCISEARCH
- 0\* FILE SYNTHLINE
- 4\* FILE TOXCENTER

0\* FILE USGENE  
42\* FILE USPATFULL  
55 FILES SEARCHED...  
0\* FILE USPATOLD  
9\* FILE USPAT2  
0\* FILE VETB  
0\* FILE VETU  
0\* FILE WATER  
1\* FILE WPIDS  
0\* FILE WPIFV  
1\* FILE WPINDEX

21 FILES HAVE ONE OR MORE ANSWERS, 63 FILES SEARCHED IN STNINDEX

L3 QUE L2 (S) (APL OR (ACUTE (2A) PROMYLELOCYTIC))

=> s L3 (s) (cancer or neoplas## or tumor?)

0\* FILE ADISCTI  
1\* FILE ADISINSIGHT  
0\* FILE ADISNEWS  
0\* FILE AGRICOLA  
0\* FILE ANABSTR  
0\* FILE ANTE  
0\* FILE AQUALINE  
0\* FILE AQUASCI  
4\* FILE BIOENG  
0\* FILE BIOSIS  
0\* FILE BIOTECHABS  
0\* FILE BIOTECHDS  
4\* FILE BIOTECHNO  
0\* FILE CABA  
0\* FILE CAPLUS  
0\* FILE CEABA-VTB  
0\* FILE CIN  
0\* FILE CONFSCI  
0\* FILE CROPB  
0\* FILE CROPU  
0\* FILE DDFB

21 FILES SEARCHED...

0\* FILE DDFU  
0\* FILE DGENE

23 FILES SEARCHED...

0\* FILE DISSABS  
0\* FILE DRUGB  
0\* FILE DRUGMONOG2  
1\* FILE DRUGU  
0\* FILE EMBAL  
0\* FILE EMBASE  
13\* FILE ESBIODASE  
0\* FILE FOMAD  
0\* FILE FROSTI  
0\* FILE FSTA  
0\* FILE GENBANK  
0\* FILE HEALSAFE  
0\* FILE IFIPAT  
0\* FILE IMSDRUGNEWS  
0\* FILE IMSPRODUCT  
0\* FILE IMSRESEARCH  
0\* FILE KOSMET  
8\* FILE LIFESCI

41 FILES SEARCHED...

```

0* FILE MEDLINE
0* FILE NTIS
0* FILE OCEAN
5* FILE PASCAL
0* FILE PCTGEN
0* FILE PROMT
0* FILE PROUSDDR
0* FILE PS
0* FILE RDISCLOSURE
0* FILE SCISEARCH
0* FILE SYNTHLINE
0* FILE TOXCENTER
0* FILE USGENE

```

54 FILES SEARCHED...

```

16* FILE USPATFULL
0* FILE USPATOLD
2* FILE USPAT2
0* FILE VETB
0* FILE VETU
0* FILE WATER
0* FILE WPIDS
0* FILE WPIFV
0* FILE WPINDEX

```

9 FILES HAVE ONE OR MORE ANSWERS, 63 FILES SEARCHED IN STNINDEX

L4 QUE L3 (S) (CANCER OR NEOPLAS## OR TUMOR?)

=> d rank

```

F1      16*  USPATFULL
F2      13*  ESBIODBASE
F3       8*  LIFESCI
F4       5*  PASCAL
F5       4*  BIOENG
F6       4*  BIOTECHNO
F7       2*  USPAT2
F8       1*  ADISINSIGHT
F9       1*  DRUGU

```

=> fil f2, f3, f5, f6

COST IN U.S. DOLLARS

| SINCE FILE | TOTAL   |
|------------|---------|
| ENTRY      | SESSION |
| 6.90       | 7.12    |

FULL ESTIMATED COST

FILE 'ESBIODBASE' ENTERED AT 08:09:24 ON 15 APR 2010

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FILE 'LIFESCI' ENTERED AT 08:09:24 ON 15 APR 2010

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FILE 'BIOENG' ENTERED AT 08:09:24 ON 15 APR 2010

COPYRIGHT (C) 2010 Cambridge Scientific Abstracts (CSA)

FILE 'BIOTECHNO' ENTERED AT 08:09:24 ON 15 APR 2010

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=> s L4

'RAR' IS NOT A VALID FIELD CODE

'RAR' IS NOT A VALID FIELD CODE  
'RAR' IS NOT A VALID FIELD CODE  
'RAR' IS NOT A VALID FIELD CODE  
L5            29 L4

=> dup rem L5  
PROCESSING COMPLETED FOR L5  
L6            14 DUP REM L5 (15 DUPLICATES REMOVED)

=> s L6 and py,2004  
L7            0 L6 AND PY,2004

=> s L6 and py<2004  
L8            6 L6 AND PY<2004

=> d L8 ibib abs 1-8

L8           ANSWER 1 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on  
             STN

ACCESSION NUMBER:        2001269487    ESBIOBASE <<LOGINID::20100415>>  
TITLE:                   Pathways of retinoic acid- or arsenic trioxide-induced  
                         PML/RAR $\alpha$  catabolism, role of oncogene degradation  
                         in disease remission  
AUTHOR(S):                Zhu, J.; Lallemand-Breitenbach, V.; De The, H.  
CORPORATE SOURCE:        Zhu, J.; Lallemand-Breitenbach, V.; De The, H.  
                         (Laboratoire associe No. 11, Affilie a l'Universite de  
                         Paris VII, Hopital St.Louis, 1, Av. C. Vellefaux, 75475  
                         Paris Cedex 10 (FR))  
SOURCE:                   Oncogene (29 Oct 2001) Volume 20, Number 49  
                         REV. IIS. 6, pp. 7257-7265, 84 refs.  
                         CODEN: ONCNES    ISSN: 0950-9232  
                         DOI: 10.1038/sj.onc.1204852  
COUNTRY OF PUBLICATION: United Kingdom  
DOCUMENT TYPE:            Journal; General Review  
LANGUAGE:                 English  
SUMMARY LANGUAGE:        English  
ENTRY DATE:               Entered STN: 1 Feb 2009  
                         Last updated on STN: 1 Feb 2009

AN           2001269487    ESBIOBASE <<LOGINID::20100415>>

AB           Although there is evidence to suggest that PML/RAR  
              $\alpha$  expression is not the sole genetic event required for the  
             development of acute promyelocytic leukemia (APL), there is  
             little doubt that the fusion protein plays a central role in the  
             initiation of leukemogenesis. The two therapeutic agents,  
             retinoic acid and arsenic, that induce clinical remissions in  
             APL, both target the oncogenic fusion protein, representing the  
             first example of oncogene-directed cancer therapy. This review  
             focuses on the molecular mechanisms accounting for PML/  
             RAR.alpha. degradation. Each drug targets a specific  
             moiety of the fusion protein (RAR $\alpha$  for retinoic acid,  
             PML for arsenic) to the proteasome. Moreover, both activate a common  
             caspase-dependent cleavage in the PML part of the fusion protein.  
             Specific molecular determinants (the AF2 transactivator domain of  
             RAR $\alpha$  for retinoic acid and the K160 SUMO-binding site in  
             PML for arsenic) are respectively implicated in RA- or arsenic-triggered  
             catabolism. The respective roles of PML/RAR.alpha.  
             activation versus its catabolism are discussed with respect to  
             differentiation or apoptosis induction in the context of single or dual  
             therapies.

L8           ANSWER 2 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on

STN

ACCESSION NUMBER: 2001269265 ESBIODASE <<LOGINID::20100415>>  
TITLE: Arsenic trioxide, a therapeutic agent for APL  
AUTHOR(S): Zhang, Ting-Dong; Chen, Guo-Qiang; Wang, Zhu-Gang;  
Wang, Zhen-Yi; Chen, Sai-Juan; Chen, Zhu  
CORPORATE SOURCE: Zhang, Ting-Dong (First Hospital, Harbin Medical  
University, 23 You Zheng Road, Nangang District,  
Harbin, 150001 (CN)); Chen, Guo-Qiang; Wang, Zhu-Gang;  
Wang, Zhen-Yi; Chen, Sai-Juan; Chen, Zhu (Shanghai  
Institute of Hematology, Rui Jin Hospital, Shanghai  
Second Medical University, 197, Rui Jin Road II,  
Shanghai 200025 (CN))  
SOURCE: Oncogene (29 Oct 2001) Volume 20, Number 49  
REV. IIS. 6, pp. 7146-7153, 73 refs.  
CODEN: ONCNES ISSN: 0950-9232  
DOI: 10.1038/sj.onc.1204762  
COUNTRY OF PUBLICATION: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 1 Feb 2009  
Last updated on STN: 1 Feb 2009

AN 2001269265 ESBIODASE <<LOGINID::20100415>>

AB Acute promyelocytic leukemia (APL) is an interesting model in  
cancer research, because it can respond to the  
differentiation/apoptosis induction therapy using all-trans  
retinoic acid (ATRA) and arsenic trioxide (AS 2 O 3 ). Over the  
past 5 years, it has been well demonstrated that AS 2 O 3 induces a  
high complete remission (CR) rate in both primary and relapsed  
APL patients (around 85~90%). The side effects are mild to  
moderate in relapsed patients, while severe hepatic lesions have been  
found in some primary cases. After CR obtained in relapsed patients,  
chemotherapy in combination with AS 2 O 3 as post-remission therapy has  
given better survival than those treated with AS 2 O 3 alone. The  
effect of AS 2 O 3 has been shown to be related to the expression of  
APL-specific PML-RAR.alpha. oncoprotein, and  
there is a synergistic effect between AS 2 O 3 and ATRA in an  
APL mouse model. Cell biology studies have revealed that AS 2 O  
3 exerts dose-dependent dual effects on APL cells. Apoptosis  
is evident when cells are treated with 0.5~2.0 µM of AS 2 O 3 while  
partial differentiation is observed using low concentrations (0.1~0.5  
µM) of the drug. The apoptosis-inducing effect is associated with the  
collapse of mitochondrial transmembrane potentials in a thiol-dependent  
manner, whereas the mechanisms underlying APL cell  
differentiation induced by low dose arsenic remain to be explored.  
Interestingly, AS 2 O 3 over a wide range of concentration (0.1~2.0  
µM) induces degradation of a key leukemogenic protein,  
PML-RAR.alpha., as well as the wild-type PML, thus  
setting up a good example of targeting therapy for human cancers  
.

L8 ANSWER 3 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on  
STN

ACCESSION NUMBER: 2001191720 ESBIODASE <<LOGINID::20100415>>  
TITLE: A novel differentiation-inducing therapy for acute  
promyelocytic leukemia with a combination of arsenic  
trioxide and GM-CSF  
AUTHOR(S): Muto, A.; Kizaki, M.; Kawamura, C.; Matsushita, H.;  
Fukuchi, Y.; Ikeda, Y.; Umezawa, A.; Yamada, T.; Hata,  
J.; Hozumi, N.; Yamato, K.; Ito, M.; Ueyama, Y.  
CORPORATE SOURCE: Muto, A.; Kizaki, M.; Kawamura, C.; Matsushita, H.;

Fukuchi, Y.; Ikeda, Y. (Department of Internal Medicine, Division of Hematology, Keio University School of Medicine, Tokyo (JP)); Umezawa, A.; Yamada, T.; Hata, J. (Department of Pathology, Division of Hematology, Keio University School of Medicine, Tokyo (JP)); Hozumi, N. (Institute of Biological Science, Science University of Tokyo, Chiba (JP)); Yamato, K. (Department of Oral Function Restitution, Division of Oral Health Sciences, Tokyo Medical and Dental University, Tokyo (JP)); Ito, M. (Central Institute for Experimental Animals, Kanagawa (JP)); Ueyama, Y. (Department of Pathology, Tokai University, School of Medicine, Kanagawa (JP))

SOURCE: Leukemia (2001) Volume 15, Number 8, pp. 1176-1184, 44 refs.

CODEN: LEUKED ISSN: 0887-6924

DOI: 10.1038/sj.leu.2402162

COUNTRY OF PUBLICATION: United Kingdom

DOCUMENT TYPE: Journal; Article

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 1 Feb 2009

Last updated on STN: 1 Feb 2009

AN 2001191720 ESBIODASE <<LOGINID::20100415>>

AB Arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) effectively induces clinical remission via apoptosis in relapsed acute promyelocytic leukemia (APL). However, because this new anti-leukemic drug is also considered to be a poison, its possible adverse effects are a highly important issue related to its clinical use. We here investigated, both in vitro and in vivo, the effects of a combination of As<sub>2</sub>O<sub>3</sub> and GM-CSF as a novel therapeutic approach for the treatment of APL. Treatment of both retinoic acid (RA)-sensitive and -resistant APL cell lines (NB4 and UF-1 cells, respectively), as well as primary APL cells with a combination of As<sub>2</sub>O<sub>3</sub> and GM-CSF for 4 days resulted in inducing differentiation, but not apoptosis, to mature granulocytes. In addition, a combination of both agents induced degradation of the PML/RAR.alpha. protein. GM-CSF was found to be associated with increased tyrosine phosphorylation of Jak2 kinase in both NB4 and UF-1 cells, and a specific inhibitor of Jak2, AG490, completely blocked the ability of GM-CSF to prevent apoptosis and induce differentiation of As<sub>2</sub>O<sub>3</sub>-treated UF-1 cells. In in vivo analysis, As<sub>2</sub>O<sub>3</sub> induced differentiation of APL cells in a RA-resistant APL model of human GM-CSF-producing transgenic SCID mice that had a high level of human GM-CSF in their sera. In contrast, As<sub>2</sub>O<sub>3</sub> alone diminished tumors in UF-1 cells transplanted into NOD/SCID mice via induction of apoptosis. In conclusion, a combination of As<sub>2</sub>O<sub>3</sub> and GM-CSF appears to be a novel differentiation-inducing therapy in patients with APL, including relapsed or RA-resistant cases.

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ACCESSION NUMBER: 2001037372 ESBIODASE <<LOGINID::20100415>>

TITLE: Granulocytic differentiation of human NB4 promyelocytic leukemia cells induced by all-trans retinoic acid metabolites

AUTHOR(S): Idres, N.; Benoit, G.; Flexor, M.A.; Lanotte, M.; Chabot, G.G.

CORPORATE SOURCE: Idres, N.; Benoit, G.; Flexor, M.A.; Lanotte, M.; Chabot, G.G. (Inst. Universitaire d'Hematologie, INSERM U496, Hopital Saint-Louis, 1 avenue Claude-Vellefaux,

SOURCE: 75475 Paris (Cedex 10) (FR))  
Cancer Research (15 Jan 2001) Volume 61,  
Number 2, pp. 700-705, 53 refs.  
CODEN: CNREA8 ISSN: 0008-5472

COUNTRY OF PUBLICATION: United States of America

DOCUMENT TYPE: Journal; Article

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 1 Feb 2009

Last updated on STN: 1 Feb 2009

AN 2001037372 ESBIODASE <<LOGINID::20100415>>

AB The metabolism of all-trans retinoic acid (ATRA) has been reported to be partly responsible for the in vivo resistance to ATRA seen in the treatment of human acute promyelocytic leukemia (APL). However, ATRA metabolism appears to be involved in the growth inhibition of several cancer cell lines in vitro. The purpose of this study was to evaluate the in vitro activity of the principal metabolites of ATRA [4-hydroxyretinoic acid (4-OH-RA), 18-hydroxyretinoic acid (18-OH-RA), 4-oxo-retinoic acid (4-oxo-RA), and 5,6-epoxy-retinoic acid (5,6-epoxy-RA)] in NB4, a human promyelocytic leukemia cell line that exhibits the APL diagnostic t(15;17) chromosomal translocation and expresses the PML-RAR.alpha. fusion protein. We established that the four ATRA metabolites were indeed formed by the NB4 cells in vitro. NB4 cell growth was inhibited (69-78% at 120 h) and cell cycle progression in the G1 phase (82-85% at 120 h) was blocked by ATRA and all of the metabolites at 1 µM concentration. ATRA and its metabolites could induce NB4 cells differentiation with similar activity, as evaluated by cell morphology, by the nitroblue tetrazolium reduction test (82-88% at 120 h) or by the expression of the maturation specific cell surface marker CD11c. In addition, nuclear body reorganization to macropunctated structures, as well as the degradation of PML-RAR.mu., was found to be similar for ATRA and all of its metabolites. Comparison of the relative potency of the retinoids using the nitroblue tetrazolium reduction test showed effective concentrations required to differentiate 50% of cells in 72 h as follows: ATRA, 15.8 ± 1.7 nM; 4-oxo-RA, 38.3 ± 1.3 nM; 18-OH-RA, 55.5 ± 1.8 nM; 4-OH-RA, 79.8 ± 1.8 nM; and 5,6-epoxy-RA, 99.5 ± 1.5 nM. The ATRA metabolites were found to exert their differentiation effects via the RARα nuclear receptors, because the RARα-specific antagonist BMS614 blocked metabolite-induced CD11c expression in NB4 cells. These data demonstrate that the principal ATRA Phase 1 metabolites can elicit leukemia cell growth inhibition and differentiation in vitro through the RARα signaling pathway, and they suggest that these metabolites may play a role in ATRA antileukemic activity in vivo.

L8 ANSWER 5 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2000114309 ESBIODASE <<LOGINID::20100415>>

TITLE: Arsenic trioxide therapy for relapsed acute promyelocytic leukemia: An useful salvage therapy

AUTHOR(S): Huang, Shang-Yi; Chen, Yao-Chang; Yang, Chih-Hsin

CORPORATE SOURCE: Huang, Shang-Yi; Chen, Yao-Chang (Department of Internal Medicine, National Taiwan University Hospital, Taipei (TW)); Chen, Yao-Chang (Department of Laboratory Medicine, National Taiwan University Hospital, Taipei (TW)); Chen, Yao-Chang (Departments of Internal Medicine, Laboratory Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei (TW)); Yang, Chih-Hsin (Department of Oncology,

SOURCE: National Taiwan University Hospital, Taipei (TW))  
 EMAIL: ycchen1@ha.mc.ntu.edu.tw  
 Leukemia and Lymphoma (2000) Volume 38,  
 Number 3-4, pp. 283-293, 72 refs.  
 CODEN: LELYEA ISSN: 1042-8194

COUNTRY OF PUBLICATION: United Kingdom  
 DOCUMENT TYPE: Journal; Article  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 31 Jan 2009  
 Last updated on STN: 31 Jan 2009

AN 2000114309 ESBIODASE <<LOGINID::20100415>>  
 AB Arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) was recently identified as a very potent agent against acute promyelocytic leukemia (APL). Intravenous infusion of 10 mg As<sub>2</sub>O<sub>3</sub> daily for one to two months can induce significant complete remission (CR) of APL, and there is no cross drug-resistance between As<sub>2</sub>O<sub>3</sub> and other antileukemic agents, including all-trans retinoic acid (ATRA). The CR rate of relapsed and/or refractory APL patients who received As<sub>2</sub>O<sub>3</sub> treatment ranged from 52.3% to 93.3%. The median duration to CR ranged from 38 to 51 days, with accumulative As<sub>2</sub>O<sub>3</sub> dosage of 340-430 mg. Although most adverse reactions of As<sub>2</sub>O<sub>3</sub> treatment were tolerable, certain infrequent but severe toxicities related to As<sub>2</sub>O<sub>3</sub> were observed, including renal failure, hepatic damage, cardiac arrhythmia and chronic neuromuscular degeneration, which should be monitored carefully. As<sub>2</sub>O<sub>3</sub> can induce partial differentiation and subsequent apoptosis of APL cells through degradation of wild type PML and PML/RAR  $\alpha$  chimeric proteins and possible anti-mitochondrial effects. Like the treatment of ATRA in APL, early relapses from As<sub>2</sub>O<sub>3</sub> treatment within a few months were not infrequently seen, indicating that rapid emerging resistance to As<sub>2</sub>O<sub>3</sub> can occur. Nevertheless, the PML/RAR  $\alpha$  fusion protein was reported to disappear in some APL patients who received As<sub>2</sub>O<sub>3</sub>, and who might earn long-survival. However, the follow-up is still too short to draw the conclusion. Intriguingly, it has been shown that As<sub>2</sub>O<sub>3</sub> can also induce apoptosis of other non-APL tumor cells with clinical achievable concentrations. However, the detailed molecular mechanisms are not yet fully understood. Further studies regarding to the pharmacological characters, clinical efficacies, toxicities, apoptogenic mechanisms, and spectrum of anti-tumor activity of As<sub>2</sub>O<sub>3</sub> are warranted.

L8 ANSWER 6 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 1998037033 ESBIODASE <<LOGINID::20100415>>  
 TITLE: Acute promyelocytic leukemia: Cellular and molecular basis of differentiation and apoptosis  
 AUTHOR(S): Chen, Zhu; Wang, Zhen-Yi; Chen, Sai-Juan  
 CORPORATE SOURCE: Chen, Zhu; Wang, Zhen-Yi; Chen, Sai-Juan (Shanghai Institute of Hematology, Ruljin Hospital, Shanghai Second Medical University, 197 Ruljin Road II, Shanghai, 200025 (CN)); Chen, Zhu (Shanghai Life Science Center, 320 Yue Yang Road, Shanghai, 200031 (CN))

SOURCE: Pharmacology and Therapeutics (Nov 1997)  
 Volume 76, Number 1-3, pp. 141-149, 56 refs.  
 CODEN: PHTHDT ISSN: 0163-7258  
 DOI: 10.1016/S0163-7258(97)00090-9

PUBL. ITEM IDENTIFIER: S0163725897000909  
 COUNTRY OF PUBLICATION: United States of America  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English

SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 31 Jan 2009  
Last updated on STN: 31 Jan 2009

AN 1998037033 ESBIOBASE <<LOGINID::20100415>>  
AB Acute promyelocytic leukemia (APL) accounts for about 10% of all acute myeloid leukemias and is characterized by the chromosomal translocation t(15;17), which fuses the retinoic acid receptor (RAR)  $\alpha$  gene to the promyelocytic leukemia (PML) gene. The PML-RAR  $\alpha$  fusion gene plays an important role in leukemogenesis through antagonizing retinoic acid signalling and the regulatory pathways mediated by PML. APL is the first example of a human cancer that can be effectively treated with the differentiation inducer all-trans retinoic acid (ATRA). The therapeutic effect of ATRA in APL has been associated with the direct modulation of PML-RAR  $\alpha$ , the restoration of the differentiation pathways regulated by wild-type RAR/retinoid X receptor heterodimer and PML. More recently, a second drug, arsenic trioxide (As<sub>2</sub>O<sub>3</sub>), has been discovered in China that also has a strong therapeutic effect against APL. As<sub>2</sub>O<sub>3</sub> can induce clinical remission in de novo or relapsed APL patients and has no cross-resistance with ATRA. It has dual effects on APL cells: preferential apoptosis at high concentration (0.5-2  $\mu$ M) and partial differentiation at low concentration (0.1-0.5  $\mu$ M). Modulation and degradation of PML-RAR  $\alpha$  proteins can be induced by As<sub>2</sub>O<sub>3</sub> and probably contribute to these two effects. These studies lead to a model in which PML-RAR  $\alpha$  could be the target of both ATRA differentiation therapy and As<sub>2</sub>O<sub>3</sub> apoptosis therapy.

=> index bioscience

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS

| SINCE FILE | TOTAL   |
|------------|---------|
| ENTRY      | SESSION |
| 24.27      | 31.39   |

FULL ESTIMATED COST

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 08:10:41 ON 15 APR 2010

63 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view search error messages that display as 0\* with SET DETAIL OFF.

=> s lysosom? (s) destabiliz?

|     |                 |
|-----|-----------------|
| 13  | FILE AGRICOLA   |
| 29  | FILE AQUALINE   |
| 48  | FILE AQUASCI    |
| 28  | FILE BIOENG     |
| 228 | FILE BIOSIS     |
| 9   | FILE BIOTECHABS |
| 9   | FILE BIOTECHDS  |
| 39  | FILE BIOTECHNO  |
| 35  | FILE CABA       |
| 273 | FILE CAPLUS     |
| 2   | FILE CONFSCI    |
| 2   | FILE CROPU      |
| 1   | FILE DDFB       |
| 19  | FILE DDFU       |

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19  FILE DGENE
22  FILE DISSABS
1  FILE DRUGB
31  FILE DRUGU
2  FILE EMBAL
203 FILE EMBASE
175 FILE ESBIODBASE
2  FILE FSTA
3  FILE GENBANK
1  FILE HEALSAFE
2  FILE IFIPAT
1  FILE KOSMET
114 FILE LIFESCI
186 FILE MEDLINE
26  FILE OCEAN
77  FILE PASCAL
2  FILE PROUDDDR
194 FILE SCISEARCH
346 FILE TOXCENTER
177 FILE USPATFULL
29  FILE USPAT2
1  FILE VETU
59 FILES SEARCHED...
29  FILE WATER
7  FILE WPIDS
7  FILE WPINDEX

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39 FILES HAVE ONE OR MORE ANSWERS, 63 FILES SEARCHED IN STNINDEX

L9 QUE LYSOSOM? (S) DESTABILIZ?

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=> s L9 (s) retin###
1  FILE AGRICOLA
1  FILE BIOENG
1  FILE BIOSIS
2  FILE BIOTECHABS
2  FILE BIOTECHDS
2  FILE CABA
3  FILE CAPLUS
1  FILE DDFB
2  FILE DDFU
1  FILE DRUGB
2  FILE DRUGU
1  FILE EMBASE
4  FILE ESBIODBASE
5  FILE LIFESCI
1  FILE MEDLINE
6  FILE PASCAL
1  FILE SCISEARCH
2  FILE TOXCENTER
17  FILE USPATFULL
5  FILE USPAT2
1  FILE WPIDS
62 FILES SEARCHED...
1  FILE WPINDEX

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22 FILES HAVE ONE OR MORE ANSWERS, 63 FILES SEARCHED IN STNINDEX

L10 QUE L9 (S) RETIN###

=> s L9 (s) (cancer or neoplas## or tumor?)

3 FILE BIOENG  
7 FILE BIOSIS  
3 FILE BIOTECHABS  
3 FILE BIOTECHDS  
3 FILE BIOTECHNO  
15 FILE CAPLUS  
6 FILE DDFU  
8 FILE DGENE

23 FILES SEARCHED...

4 FILE DISSABS  
7 FILE DRUGU  
9 FILE EMBASE  
18 FILE ESBIODBASE  
11 FILE LIFESCI  
9 FILE MEDLINE  
9 FILE PASCAL  
2 FILE PROUSDDR

49 FILES SEARCHED...

9 FILE SCISEARCH  
10 FILE TOXCENTER  
43 FILE USPATFULL  
10 FILE USPAT2  
2 FILE WPIDS  
2 FILE WPINDEX

22 FILES HAVE ONE OR MORE ANSWERS, 63 FILES SEARCHED IN STNINDEX

L11 QUE L9 (S) (CANCER OR NEOPLAS## OR TUMOR?)

=> s L11 and (stain### or mark### or releas###)

1 FILE BIOENG  
3 FILE BIOSIS  
1 FILE BIOTECHABS  
1 FILE BIOTECHDS  
2 FILE BIOTECHNO  
5 FILE CAPLUS

15 FILES SEARCHED...

1 FILE DDFU

23 FILES SEARCHED...

2 FILE DISSABS  
5 FILE DRUGU  
4 FILE EMBASE  
11 FILE ESBIODBASE

34 FILES SEARCHED...

6 FILE LIFESCI  
4 FILE MEDLINE  
5 FILE PASCAL  
4 FILE SCISEARCH  
4 FILE TOXCENTER

53 FILES SEARCHED...

41 FILE USPATFULL  
9 FILE USPAT2  
1 FILE WPIDS  
1 FILE WPINDEX

20 FILES HAVE ONE OR MORE ANSWERS, 63 FILES SEARCHED IN STNINDEX

L12 QUE L11 AND (STAIN### OR MARK### OR RELEAS###)

=> d rank

|     |    |            |
|-----|----|------------|
| F1  | 41 | USPATFULL  |
| F2  | 11 | ESBIOBASE  |
| F3  | 9  | USPAT2     |
| F4  | 6  | LIFESCI    |
| F5  | 5  | CAPLUS     |
| F6  | 5  | DRUGU      |
| F7  | 5  | PASCAL     |
| F8  | 4  | EMBASE     |
| F9  | 4  | MEDLINE    |
| F10 | 4  | SCISEARCH  |
| F11 | 4  | TOXCENTER  |
| F12 | 3  | BIOSIS     |
| F13 | 2  | BIOTECHNO  |
| F14 | 2  | DISSABS    |
| F15 | 1  | BIOENG     |
| F16 | 1  | BIOTECHABS |
| F17 | 1  | BIOTECHDS  |
| F18 | 1  | DDFU       |
| F19 | 1  | WPIDS      |
| F20 | 1  | WPINDEX    |

=> fil f2, f4, f5, f8-f17

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=> s L12  
9 FILES SEARCHED...  
L13 47 L12

=> dup rem L13  
PROCESSING COMPLETED FOR L13  
L14 16 DUP REM L13 (31 DUPLICATES REMOVED)

=> s L14 and py<2004  
6 FILES SEARCHED...  
L15 5 L14 AND PY<2004

=> d L15 ibib abs 1-5

L15 ANSWER 1 OF 5 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on  
STN

ACCESSION NUMBER: 2003003379 ESBIODBASE <<LOGINID::20100415>>  
TITLE: Pyridoxal isonicotinoyl hydrazone analogs induce  
apoptosis in hematopoietic cells due to their  
iron-chelating properties  
AUTHOR(S): Buss, Joan L.; Ponka, Prem; Neuzil, Jiri; Gellert,  
Nina; Weber, Christian  
CORPORATE SOURCE: Buss, Joan L.; Ponka, Prem (Department of Physiology,  
McGill University, Sir M. B. Davis Jewish Gen.  
Hospital, 3755 chemin de la Cote-Ste-Catherine,  
Montreal, Que. H3T 1E2 (CA)); Neuzil, Jiri (Division of  
Pathology II, Faculty of Health Sciences, University  
Hospital, Linkoping (SE)); Neuzil, Jiri; Gellert, Nina;  
Weber, Christian (Inst. for Prev. of Cardiovasc. Dis.,  
Ludwig Maximilians University, Munich (DE)); Neuzil,  
Jiri (Heart Foundation Research Center, School of  
Health Sciences, Griffith University, Southport, QLD  
(AU)); Weber, Christian (Dept. of Cardiovasc. Molec.  
Biology, University Hospital, Aachen (DE))  
EMAIL: prem.ponka@mcgill.ca  
SOURCE: Biochemical Pharmacology (15 Jan 2003) Volume  
65, Number 2, pp. 161-172, 44 refs.  
CODEN: BCPA6 ISSN: 0006-2952  
DOI: 10.1016/S0006-2952(02)01512-5  
PUBL. ITEM IDENTIFIER: S0006295202015125  
COUNTRY OF PUBLICATION: United States of America  
DOCUMENT TYPE: Journal; Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 2 Feb 2009  
Last updated on STN: 2 Feb 2009

AN 2003003379 ESBIODBASE <<LOGINID::20100415>>

AB Analog of pyridoxal isonicotinoyl hydrazone (PIH) are of interest as  
iron chelators for the treatment of secondary iron overload and  
cancer. PIH, salicylaldehyde isonicotinoyl hydrazone (SIH), and  
2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone (NIH), the toxicity  
of which varies over two orders of magnitude, were selected for a study of  
their mechanisms of toxicity. PIH analogs and their iron complexes  
caused concentration- and time-dependent apoptosis in Jurkat T  
lymphocytes and K562 cells. Bcl-2 overexpression was partially

anti-apoptotic, suggesting mitochondrial mediation of apoptosis. Since the pan-caspase inhibitor zVAD-fmk did not reduce lysosomal and mitochondrial destabilization, these events occur upstream of caspase activation. In contrast, phosphatidylserine externalization and the development of apoptotic morphology were inhibited significantly, indicating the role of caspases in mediating these later events. Since overexpression of CrmA had no effect on apoptosis, caspase-8 is not likely involved. Fe 3+ complexes of SIH and NIH, which accumulated in 59 Fe-labeled mouse reticulocytes during incubation with the chelators, also caused apoptosis. BSA, which promotes release of the complexes from cells, reduced the toxicity of SIH and NIH, suggesting that the induction of apoptosis by PIH analogs involves toxic effects mediated by their Fe 3+ complexes. Moreover, analogs of these agents lacking the iron-chelating moiety were non-toxic. .COPYRG. 2002 Published by Elsevier Science Inc.

L15 ANSWER 2 OF 5 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2002214115 ESBIODASE <<LOGINID::20100415>>  
 TITLE: Tumor necrosis factor- $\alpha$ -associated lysosomal permeabilization is cathepsin B dependent  
 AUTHOR(S): Werneburg, Nathan W.; Guicciardi, M. Eugenia; Bronk, Steven F.; Gores, Gregory J.  
 CORPORATE SOURCE: Werneburg, Nathan W.; Guicciardi, M. Eugenia; Bronk, Steven F.; Gores, Gregory J. (Mayo Med. School, Clinic/Foundation, 200 First St. SW, Rochester, MN 55905 (US))  
 SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology (Oct 2002) Volume 283, Number 4 46-4, 44 refs.  
 CODEN: APGPDF ISSN: 0193-1857  
 COUNTRY OF PUBLICATION: United States of America  
 DOCUMENT TYPE: Journal; Article  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 1 Feb 2009  
 Last updated on STN: 1 Feb 2009

AN 2002214115 ESBIODASE <<LOGINID::20100415>>  
 AB Cathepsin B (Cat B) is released from lysosomes during tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) cytotoxic signaling in hepatocytes and contributes to cell death. Sphingosine has recently been implicated in lysosomal permeabilization and is increased in the liver by TNF- $\alpha$ . Thus the aims of this study were to examine the mechanisms involved in TNF- $\alpha$ -associated lysosomal permeabilization, especially the role of sphingosine. Confocal microscopy demonstrated Cat B-green fluorescent protein and LysoTracker Red were both released from lysosomes after treatment of McNTcp.24 cells with TNF- $\alpha$ /actinomycin D, a finding compatible with lysosomal destabilization. In contrast, endosomes labeled with Texas Red dextran remained intact, suggesting lysosomes were specifically targeted for permeabilization. LysoTracker Red was released from lysosomes in hepatocytes treated with TNF- $\alpha$  or sphingosine in Cat B(+/+) but not Cat B(-/-) hepatocytes, as assessed by a fluorescence-based assay. With the use of a calcein release assay in isolated lysosomes, sphingosine permeabilized liver lysosomes isolated from Cat B(+/+) but not Cat B(-/-) liver. C 6 ceramide did not permeabilize lysosomes. In conclusion, these data implicate a sphingosine-Cat B interaction inducing lysosomal destabilization during TNF- $\alpha$  cytotoxic signaling.

L15 ANSWER 3 OF 5 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2002107688 ESBIODASE <<LOGINID::20100415>>  
TITLE: Lysosomal destabilization in p53-induced apoptosis  
AUTHOR(S): Yuan, Xi-Ming; Li, Wei; Brunk, Ulf T.; Dalen, Helge; Lotem, Joseph; Kama, Rachel; Sachs, Leo  
CORPORATE SOURCE: Yuan, Xi-Ming; Li, Wei; Brunk, Ulf T. (Pathology II, Linkoping University, Linkoping 581 85 (SE)); Dalen, Helge (Department of Pathology, Gade Institute, University of Bergen, Bergen N-5021 (NO)); Lotem, Joseph; Kama, Rachel; Sachs, Leo (Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100 (IL))  
EMAIL: yuan.ximing@inr.liu.se  
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (30 Apr 2002) Volume 99, Number 9, pp. 6286-6291, 59 refs.  
CODEN: PNASA6 ISSN: 0027-8424  
DOI: 10.1073/pnas.092135599  
COUNTRY OF PUBLICATION: United States of America  
DOCUMENT TYPE: Journal; Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 1 Feb 2009  
Last updated on STN: 1 Feb 2009

AN 2002107688 ESBIODASE <<LOGINID::20100415>>

AB The tumor suppressor wild-type p53 can induce apoptosis. M1-t-p53 myeloid leukemic cells have a temperature-sensitive p53 protein that changes its conformation to wild-type p53 after transfer from 37°C to 32°C. We have now found that these cells showed an early lysosomal rupture after transfer to 32°C. Mitochondrial damage, including decreased membrane potential and release of cytochrome c, and the appearance of apoptotic cells occurred later. Lysosomal rupture, mitochondrial damage, and apoptosis were all inhibited by the cytokine IL-6. Some other compounds can also inhibit apoptosis induced by p53. The protease inhibitor N-tosyl-L-phenylalanine chloromethyl ketone inhibited the decrease in mitochondrial membrane potential and cytochrome c release, the Ca<sup>2+</sup>-ATPase inhibitor thapsigargin inhibited only cytochrome c release, and the antioxidant butylated hydroxyanisole inhibited only the decrease in mitochondrial membrane potential. In contrast to IL-6, these other compounds that inhibited some of the later occurring mitochondrial damage did not inhibit the earlier p53-induced lysosomal damage. The results indicate that apoptosis is induced by p53 through a lysosomal-mitochondrial pathway that is initiated by lysosomal destabilization, and that this pathway can be dissected by using different apoptosis inhibitors. These findings on the induction of p53-induced lysosomal destabilization can also help to formulate new therapies for diseases with apoptotic disorders.

L15 ANSWER 4 OF 5 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 1998098745 ESBIODASE <<LOGINID::20100415>>  
TITLE: Chromosomal instability is correlated with telomere erosion and inactivation of G2 checkpoint function in human fibroblasts expressing human papillomavirus type 16 E6 oncoprotein  
AUTHOR(S): Filatov, Leonid; Golubovskaya, Vita; Hurt, John C.; Byrd, Laura L.; Phillips, Jonathan M.; Kaufmann,

CORPORATE SOURCE: William K.  
Filatov, Leonid; Golubovskaya, Vita; Hurt, John C.;  
Byrd, Laura L.; Phillips, Jonathan M.; Kaufmann,  
William K. (Dept. of Pathol. and Lab. Medicine,  
Lineberger Compreh. Cancer Center, Univ. of N. Carolina  
at Chapel Hill, Chapel Hill, NC 27599-7295 (US))  
SOURCE: Oncogene (9 Apr 1998) Volume 16, Number 14,  
pp. 1825-1838, 62 refs.  
CODEN: ONCNES ISSN: 0950-9232  
COUNTRY OF PUBLICATION: United Kingdom  
DOCUMENT TYPE: Journal; Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 31 Jan 2009  
Last updated on STN: 31 Jan 2009

AN 1998098745 ESBIODBASE <<LOGINID::20100415>>

AB Cell cycle checkpoints and tumor suppressor gene functions appear to be required for the maintenance of a stable genome in proliferating cells. In this study chromosomal destabilization was monitored in relation to telomere structure, lifespan control and G2 checkpoint function. Replicative senescence was inactivated in secondary cultures of human skin fibroblasts by expressing the human papillomavirus type 16 (HPV-16) E6 oncoprotein to inactivate p53. Chromosome aberrations were enumerated during in vitro aging of isogenic control (F5neo) and HPV-16E6-expressing (F5E6) fibroblasts. We found that structural and numerical aberrations in chromosomes were significantly increased in F5E6 cells during aging in vitro and fluorescence in situ hybridization (FISH) analysis using chromosome-specific probes demonstrated the occurrence of rearrangements involving chromosome 4 and 6 in genetically unstable F5E6 cells. Flow and karyotypic analyses revealed increased and aneuploidy in F5E6 cells only at passages > 16, although these cells displayed defective mitotic spindle checkpoint function associated with inactivation of p53 at passages 5 and 16. G2 checkpoint function was confirmed to be gradually but progressively inactivated during in vitro aging of E6-expressing cells. Aging of F5neo fibroblasts was documented during in vitro passaging by induction of a senescence-associated marker, pH 6.0 lysosomal  $\beta$ -galactosidase. F5E6 cells displayed extension of in vitro lifespan and did not induce  $\beta$ -galactosidase at high passage. Erosion of telomeres during in vitro aging of telomerase-negative F5neo cells was demonstrated by Southern hybridization and by quantitative FISH analysis on an individual cell level. Telomeric signals diminished continuously as F5neo cells aged in vitro being reduced by 80% near the time of replicative senescence. Telomeric signals detected by FISH also decreased continuously during aging of telomerase-negative F5E6 cells, but telomeres appeared to be stabilized at passage 34 when telomerase was expressed. Chromosomal instability in E6-expressing cells was correlated ( $P < 0.05$ ) with both loss of telomeric signals and inactivation of G2 checkpoint function. The results suggest that chromosomal stability depends upon a complex interaction among the systems of telomere length maintenance and cell cycle checkpoints.

L15 ANSWER 5 OF 5 DISSABS COPYRIGHT (C) 2010 ProQuest Information and Learning Company; All Rights Reserved on STN

ACCESSION NUMBER: 95:48382 DISSABS Order Number: AAI9527197

TITLE: DELIVERY OF MACROMOLECULES BY CATIONIC LIPOSOMES (DIOLEOYL PHOSPHATIDYLETHANOLAMINE)

AUTHOR: FARHOOD, HASSAN M. F. [PH.D.]; HUANG, LEAF [advisor]

CORPORATE SOURCE: THE UNIVERSITY OF TENNESSEE (0226)

SOURCE: Dissertation Abstracts International, (1994) Vol.

56, No. 4B, p. 1784. Order No.: AAI9527197. 169 pages.  
DOCUMENT TYPE: Dissertation  
FILE SEGMENT: DAI  
LANGUAGE: English  
ENTRY DATE: Entered STN: 19951031  
Last Updated on STN: 19951031

AB        Delivery of macromolecules to mammalian cells is a critical step for gene expression studies and for gene therapy. Cationic liposomes are simple vehicles for delivering macromolecules efficiently, reproducibly, and safely. To improve the efficiency and minimize the toxicity of cationic liposomes, liposomes containing cationic cholesterol derivatives and the phospholipid dioleoyl phosphatidyl-ethanolamine (DOPE) were designed and tested in transfection assays. Derivatives with a tertiary amine head group had efficient transfection activity, negligible cytotoxicity, and no protein kinase C-inhibition activity, while derivatives with a quaternary amine head group had no transfection activity, higher toxicity, and protein kinase C-inhibition activity. The membrane stabilizing phospholipid, dioleoyl phosphatidylcholine (DOPC), did not replace DOPE (a membrane destabilizer) in transfection. A new DNA delivery assay was developed that demonstrated the qualitative and quantitative requirement for DOPE in cationic liposome mediated transfection. The lysosomotropic agent chloroquine inhibition of transfection suggested that endocytosis is the major route of DNA delivery by cationic liposomes. Cationic liposomes were also used to deliver of the human immunodeficiency virus-1 trans-activator protein (tat), a model transcription factor that induces the expression of genes under the control of the virus promoter. Tat inefficient entry into the cytosolic compartment was improved with different cationic liposome formulations. Tat delivery was allowed by the inclusion of DOPE, but not DOPC, in the liposome formulations. Co-internalization of tat and cationic liposomes was required for maximal delivery activity implicating a common endocytic compartment from which tat was released into the cytosol, a conclusion based on the known membrane-disrupting function of DOPE and the natural endocytic fate of tat. To test the possibility of DNA and protein co-delivery, cells were transfected with tat protein complexed to a tat-responsive reporter DNA and cationic liposomes. The gene induction level was high and specific to tat-responsive promoter and the co-delivery system was applicable to different cell types using different cationic liposome formulations. This co-delivery strategy may be useful where transient and maximum gene expression may be necessary in certain applications such as cancer gene therapy.

=> logoff